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PERSPECTIVE

Mysteries of type 2 diabetes: the Indian Elephant meets the Chinese Dragon

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INTRODUCTION

China and India offer a compelling country comparison to explore drivers and solutions to the type 2 diabetes epidemic. They are the world's most populated countries and fastest growing major economies.[1–3] Both countries are also confronting a growing burden of type 2 diabetes.

The prevalence of diabetes has tripled in China and nearly doubled in India in less than two decades.[1] China now leads the world in terms of the number of people with diabetes (109.6 million adults (11%)), and India is second with ~69.2 million adults (9%) with diabetes.[1] By 2040, the number of people with diabetes in China and India is projected to reach 150.7 million and 123.5 million, respectively.[1] Diabetes is a major cause of morbidity and mortality, and given the high health-care expenditures and lost work productivity associated with the disease, it poses a great threat to future economic development.[1,2]

We therefore explore similarities in the etiology and pathophysiology of type 2 diabetes in China and India, and present the major risk factors in these two countries, with a primary focus on: (i) rapid economic development, unplanned urbanization and dramatic lifestyle changes; (ii) innate susceptibility to early decline in β-cell function in addition to a propensity for insulin resistance; and (iii) early life factors, including *in utero* undernutrition and overnutrition. Finally, we present opportunities for collaborative research and evidence-based action to address the diabetes epidemic.

SHARED ETIOLOGY FOR TYPE 2 DIABETES

Many risk factors are contributing to the rise in the prevalence of diabetes globally (see Table 1). In low- and middle-income countries (LMICs), the relative contribution of risk factors to the diabetes epidemic may be different than in high-income countries, and additional risk factors may be operational. Here, we discuss the commonalities in the etiology and pathophysiology of type 2 diabetes in China and India and present a summary of risk factors for diabetes that may be of particular importance in both countries (see Table 2).

Economic development, unplanned urbanization and lifestyle changes

Economic development, unplanned urbanization and accompanying shifts in physical activity, diet and obesity are key drivers of type 2 diabetes globally, and are rapidly increasing concurrently in both China and India[3] (Figure 1). The growth of cities without planned infrastructure to facilitate walking and cycling for transport, promote recreational physical activity and reduce sedentary time in cars constrains opportunities for active lifestyles.[4] Between 1991 and 2011, the metabolic equivalent of task minutes per week in China fell from 420 to 243 among women and 382 to 264 among men.[5] In the 1990s, motorization expanded quickly in China and obesity among men whose households acquired a motor vehicle increased twofold.[4] Over the past three decades, China and India have also undergone a nutrition transition resulting in changes in dietary patterns, namely increased energy intake from dietary fat, animal products, refined carbohydrates, and sugar-sweetened beverages and decreased consumption of cereals.[5,6] Taken together, these rapid declines in physical activity and dietary shifts are major factors contributing to the rise in obesity and subsequent type 2 diabetes epidemic in China and India. At a time of dynamic social and economic changes, the relationship between socioeconomic status and diabetes in these countries is complex and not fully understood. As economies grow, the burden of obesity shifts from high-socioeconomic status to lower-socioeconomic status groups;[7,8] however, the distribution of other diabetes risk factors across socioeconomic status groups is a topic of ongoing investigation.

Pathophysiology

The pathophysiology of type 2 diabetes is complex, involving both increased insulin resistance and impaired insulin secretion.[9] Traditionally, the pathogenesis is thought to begin with obesity- and age-related insulin resistance followed by a subsequent decline in β-cell function and reduced insulin secretion, eventually leading to overt hyperglycemia.[9,10] However, evidence suggests that there are ethnic differences in the relative contributions of insulin resistance and insulin secretion in the natural history of type 2 diabetes progression.[11] Asian Indian and Chinese individuals may have an innate susceptibility for early decline in β-cell function, thereby placing them at very high risk for disease development beyond traditionally associated risk factors, such as age, adiposity and insulin resistance.

Cross-sectional studies from Chennai, India, noted that in young adults, impaired insulin secretion occurred early in the natural history of type 2 diabetes[12] and Asian Indians with mild dysglycemia had reduced insulin secretion, regardless of age, adiposity, family history of diabetes or insulin resistance.[13] A recent study in Asian Indian immigrants to the United States also found that while both insulin secretion and insulin resistance were associated with prediabetes and diabetes, insulin secretion was

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Table 1. Type 2 diabetes risk factors across the lifecourse

Risk factor	*Intrauterine*	*Early childhood*	*Childhood and adolescence*	*Adulthood*
Biology, genetics and demographic factors				
Maternal undernutrition	+	+	+	+
Placental insufficiency	+	+	+	+
Low birthweight	+	+	+	+
Maternal obesity	+	+	+	+
Maternal diabetes	+	+	+	+
Innate susceptibility to early decline in β-cell function and propensity to insulin resistance	+	+	+	+
Family history of type 2 diabetes	+	+	+	+
Cesarean section		+	+	+
Formula fed		+	+	+
Gut microbiota		+	+	+
Rapid weight gain		+	+	
Obesity		+	+	+
Inflammation				+
High blood pressure				+
History of gestational diabetes				+
Aging				+
Tuberculosis				+
Stress and psychosocial factors			+	+
PCOS			+	+
Behavioral factors				
Unhealthy diet (e.g., refined carbohydrates, excess alcohol, added sugar, red meat)		+	+	+
Consumption of sugar-sweetened beverages		+	+	+
Physical inactivity		+	+	+
Sedentary time		+	+	+
Short sleep duration				+
Depression				+
Smoking				+
Environmental factors				
Unplanned urbanization		+	+	+
Noise pollution		+	+	+
Air pollution	+	+	+	+
Persistent organic pollutants		+	+	+
Maternal stress and psychosocial factors	+	+	+	+

Abbreviations: LMIC, low- and middle-income countries; PCOS, polycystic ovary syndrome. Many risk factors—including well-established and novel risk factors—are contributing to the increase in diabetes prevalence worldwide and have a role in the epidemic of diabetes in both high-income countries and LMICs, such as China and India.[5,51]

more strongly associated, even after adjustment for visceral fat, age, family history of diabetes and hypertension.[14] These findings indicate that individuals of Asian Indian ethnicity may have innate susceptibilities for poor insulin secretion, which may be the primary factor for type 2 diabetes development in this population.

Similar findings have been noted in Chinese populations. A study in Chinese adults aged 18–80 years reported that insulin secretion adjusted for insulin sensitivity was diminished within the normal range of fasting plasma glucose. Insulin secretion was further impaired in individuals with impaired fasting glucose and overt type 2 diabetes. However, insulin sensitivity was impaired only slightly within the normal range of fasting plasma glucose and was decreased substantially in individuals with impaired fasting glucose and type 2 diabetes.[15] Thus, although insulin sensitivity and impaired insulin secretion are associated with increasing fasting plasma glucose, insulin secretion was more likely to be influenced by fasting plasma glucose changes in this population. Another study of Chinese adults found that early diabetes was characterized by increased impairments in insulin secretion rather than insulin resistance.[16] A previous study by the same group reported that 60% of participants with prediabetes had 1-h postchallenge glucose values >11.1 mmol/l and were characterized by metabolic abnormalities, which may be due to impairment of early insulin release.[17] Taken together, the results of these studies indicate that challenges in insulin secretion may occur before the onset of insulin resistance among Chinese populations.

Early life factors

Early life adverse environmental exposures are associated with increased susceptibilities for many metabolic diseases experienced in adulthood.[18] Such adverse exposures can include both *in utero* undernutrition and overnutrition, which can lead to epigenetic modifications modulating the gene/environment interactions related to disease risk.

In utero undernutrition. Nutritional deprivation *in utero* and/or low birthweight has been shown to predispose individuals to insulin resistance, reduce capacity for insulin secretion[19–21] and increase type 2 diabetes risk.[22–24] The relationship between fetal undernutrition, low birthweight and subsequent development of chronic disease may be particularly important in countries such as China and India where maternal undernutrition and low birthweight are still prevalent in both urban and rural areas. According to the 2015–2016 National Family Health Survey in India, 22.9% of women of reproductive age (15–49 years) are underweight (15.5%

Table 2. Overview of type 2 diabetes risk factors of importance in China, India and other low- and middle-income countries

Biology, genetics and demographic factors		*Burden of exposure*[a]	*Size of effect*	*Strength of evidence*[b]
Obesity	Obesity is one of the most important risk factors for type 2 diabetes, and obesity prevalence is high and increasing in China and India. In China, higher BMI has been found to be associated with higher diabetes incidence in men and women.[51] A study in Chennai, India reported a relative diabetes risk among obese adults of 2.1 (95% CI: 1.35–3.29) compared with non-obese adults[51]	High	Large	High
In utero overnutrition	Excess *in utero* nutrition, often related to maternal obesity and gestational diabetes, has been linked to higher risk of type 2 diabetes in offspring. Given the increasing prevalence of maternal obesity and gestational diabetes in Chinese and Indian populations, *in utero* overnutrition is likely to have a large, and growing, influence on the rise of type 2 diabetes	High	Large	Medium
In utero undernutrition	Nutritional deprivation *in utero* and low birthweight can predispose individuals to insulin resistance and reduced capacity for insulin secretion, thereby increasing type 2 diabetes risk. *In utero* undernutrition may be a significant driver of the type 2 diabetes epidemics in LMICs, such as China and India, that have witnessed centuries of undernutrition and continue to face high levels of maternal undernutrition and low birthweight. Given that *in utero* undernutrition is associated with increased susceptibility to diabetes through epigenetic pathways, *in utero* undernutrition can have an important part in the development of diabetes across generations	High	Medium	High
Innate susceptibility to early decline in β-cell function and propensity to insulin resistance	A growing body of research focusing on the pathophysiology of type 2 diabetes in Asian Indian and Chinese populations indicates that these populations may have an innate susceptibility for early decline in β-cell function and propensity to insulin resistance, leading to very high risk for development of type 2 diabetes	High	Medium	Low
Tuberculosis	An accumulating body of literature indicates that chronic infections, such as tuberculosis, may increase risk of type 2 diabetes, although the mechanism by which tuberculosis influences diabetes risk is not well described.[52] In India, studies have reported a higher prevalence of diabetes and prediabetes among tuberculosis patients compared with the general population.[53,54] In rural areas of China, a prospective study found that the prevalence of diabetes was significantly higher in patients with tuberculosis compared with those without.[52] India and China have the largest tuberculosis epidemics in the world. Therefore, the influence of tuberculosis on diabetes may be particularly large in these settings	High	Medium	Medium
Behavioral factors				
Unhealthy diet	China and India have undergone rapid nutrition transitions that have resulted in changes in dietary patterns, including increased energy intake from dietary fat and animal foods, higher consumption of refined carbohydrates and sugar-sweetened beverages, and decreased consumption of cereals. These dietary shifts are thought to be important contributors to the rise in diabetes prevalence in China and India	High	Medium	High
Physical inactivity	Physical inactivity is a well-established predictor of the development of type 2 diabetes. Physical activity trends between 1991 and 2011 in China show declines in occupational physical activity among men and women and domestic physical activity among women[55]	Medium	Large	High
Smoking	Smoking may be a major risk factor for diabetes in India and China, especially among men. Smoking increases diabetes risk by ~45%, and China has the highest number of smokers in the world, followed by India.[5,56] In 2011, 311 million Chinese adults were current smokers, including 295 million men (51.6%) and 16 million women (2.9%).[57] In India, more than 100 million adults smoked in 2010, with nearly one-quarter of men being current smokers[56]	High	Large	Medium

Table 2. (Continued)

Biology, genetics and demographic factors		*Burden of exposure*[a]	*Size of effect*	*Strength of evidence*[b]
Environmental factors				
Unplanned urbanization	Urban and transport planning and design influence diet and physical activity lifestyle behaviors and obesity and affect NCDs like type 2 diabetes.[4] In China and India, a lack of infrastructure to encourage physical activity and support the availability and accessibility of healthy foods combined with rapid migration to cities is likely prompting national declines in physical activity and dietary changes, and contributing to the substantial increases in obesity and type 2 diabetes[4–6]	High	Medium	Low
Air pollution	Air pollution exposure is an emerging risk factor for type 2 diabetes.[58] A recent systematic review and meta-analysis demonstrated that exposure to air pollutants was associated with a small increase in type 2 diabetes risk.[58] Air pollution may be an important contributor to type 2 diabetes in China and India, given that levels of air pollution in these countries are among the highest in the world and the populations exposed are likely massive.[58,59] More research is needed to uncover the role of outdoor air pollution-independent of urbanization, and to investigate the effects of indoor air pollution on type 2 diabetes risk for which evidence is scarce[58]	High	Small	Low

Abbreviations: BMI, body mass index; CI, confidence interval; LMIC, low- and middle-income countries; NCD, non-communicable diseases; Increasingly, research indicates that the relative contribution of risk factors to type 2 diabetes may differ in high-income countries and LMICs, and additional risk factors may be operational in LMICs.[51,60] In China and India, risk factors that may be of particular importance are given in the table. [a]Burden of exposure in China and India relative to other countries. National prevalence estimates were used to assess burden of exposure, when data were available. [b]Criteria (based on Jaacks *et al.*[51])—low: ecological studies or cross-sectional epidemiological studies; medium: prospective epidemiological studies; high: randomized controlled trials or, for biology, genetics and demographic factors, consistent observational studies.

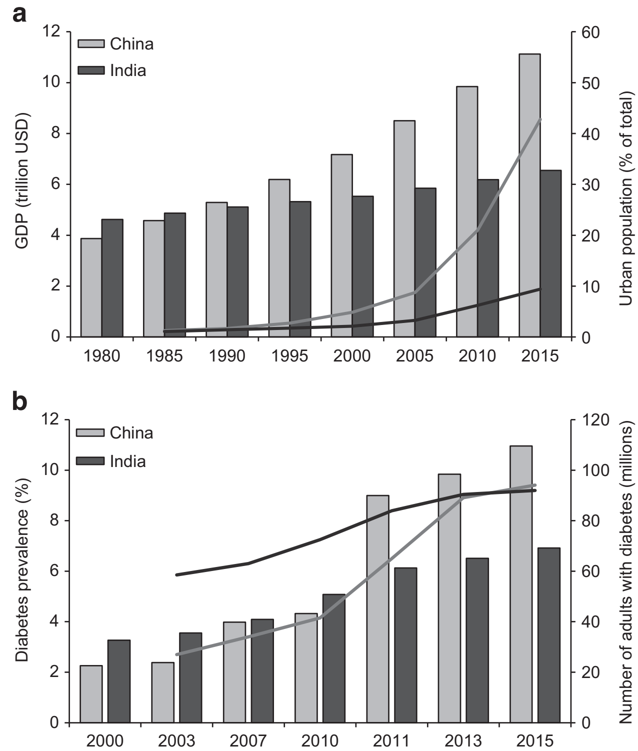

Figure 1. Trends in economic growth, urbanization and diabetes in China and India. (**a**, Y1) Gross domestic product (GDP) in China and India, 1980–2015. (**a**, Y2) Percentage of the total population living in urban areas in China and India, 1980–2015. (**b**, Y1) Prevalence of diabetes among adults (aged 20–79 years) in China and India, 2000–2015.[1] (**b**, Y2) Number of adults (aged 20–79 years) with diabetes in China and India, 2000–2015.[1]

in urban areas and 26.7% in rural areas), compared with 35.5% in 2005–2006.[25] While the situation is better in China, data also point to a high prevalence of underweight among women of reproductive age. For example, the prevalence of underweight among Chinese women aged 15 to 18 years is 17% in urban areas and 22% in rural areas.[26] Further, in rural areas in China, the underweight prevalence among women aged 19 to 49 years decreased in the 1990s and early 2000s, but has begun to increase in recent years.[27]

The prevalence of low birthweight is 31% in India[28] and 6% in China.[29] There have only been slight improvements in the prevalence of low birthweight over time, as the percentage of low-birthweight infants was 33% in India and 9% in China in 1990.[30] These individuals are now adults and may start to experience chronic diseases related to low birthweight. In turn, the large number of low-birthweight individuals born in recent years will likely contribute to the burden of type 2 diabetes in China and India in the future. Individuals who are born thin but experience rapid weight gain in childhood are also at increased risk for type 2 diabetes and impaired glucose tolerance. A longitudinal study from India that examined the incidence of impaired glucose tolerance and type 2 diabetes in a population of young adults found that those who had impaired glucose tolerance or diabetes in adulthood were thin in infancy and became overweight in early childhood as the result of accelerated gain in body mass during their formative years.[31] The occurrence of accelerated growth in childhood is a relatively new phenomenon in countries such as India and China and is likely attributable to nutrition transitions that have occurred over the past few decades.

Evidence suggests that the effect of *in utero* undernutrition on type 2 diabetes risk may not be limited to one generation.

A recent study investigating the role of fetal exposure to the Chinese famine on future type 2 diabetes risk in two generations found that in the first generation, prenatal exposure to famine was associated with an elevated risk of hyperglycemia in adulthood. Offspring of exposed individuals also had an increased risk of type 2 diabetes in adulthood, compared with those whose parents were not exposed.[32] Therefore, fetal undernutrition may have an important role in the development of type 2 diabetes across consecutive generations, and can influence the mechanistic factors behind the increased risk for type 2 diabetes in countries such as China and India.

In utero overnutrition. While the risk association of birthweight and type 2 diabetes is attributed primarily to *in utero* undernutrition and low birthweight, excess *in utero* nutrition, often related to maternal obesity and gestational diabetes, is also associated with an increased risk of diabetes in offspring.[33,34] Studies in both Chinese and Indian populations have found that the *in utero* environment of hyperinsulinemia is associated with an increased risk of cardiometabolic abnormalities in the offspring.[35–37] Therefore, the relationship between birthweight and future cardiometabolic risk is not linear, but likely to be inversely J shaped. A study comparing birthweight, risk of type 2 diabetes, abdominal obesity and hypertension among Chinese adults found that both low and high birthweight were associated with high risk of developing abdominal obesity and hypertension. However, low birthweight coupled with abdominal obesity was a stronger predictor for type 2 diabetes than high birthweight.[38] These results indicate a possibility of a differing pathogenesis of obesity and diabetes development among individuals with low and high birthweights. This is important for low- and middle-income countries (LMICs) such as India and China that are currently facing a dual burden of undernutrition and overnutrition.

Type 2 diabetes in non-overweight individuals

Novel research on type 2 diabetes in non-overweight individuals in India and China further points to a shared etiology of disease in these countries. Overweight and obesity are well-known risk factors for type 2 diabetes. However, overweight and obesity may not yet play the same role in fueling the type 2 diabetes epidemic in India and China compared with high-income countries. From an ecological perspective, India and China have the highest prevalence of type 2 diabetes worldwide,[1] but they have a greater percentage of individuals with normal body mass index (BMI) compared with the United States. In all, 62.5% of individuals in India and 58.9% of individuals in China have a BMI between 18.5 and 25 kg/m^2, as compared with 35.7% of individuals in the United States.[39] Perhaps more convincing are epidemiological studies indicating that Indian and Chinese individuals develop diabetes at much lower levels of BMI than members of other race/ethnic groups. A nationally representative study from India reported a mean BMI of 24.4 kg/m^2 in all individuals with type 2 diabetes,[40] while a nationally representative study in China reported a mean BMI of 25.2 kg/m^2 in those with newly diagnosed diabetes and 25.8 kg/m^2 in those whose diabetes was previously diagnosed.[41] This is in contrast to the mean BMI of 32.8 kg/m^2 in individuals with diagnosed diabetes in a nationally representative sample from the United States.[42] Furthermore, a cross-sectional study from Hong Kong found that 5.8% of individuals with type 2 diabetes were underweight and 30.6% were normal weight, even when using redefined World Health Organization criterion for BMI in Asian populations.[43]

While overweight and obesity are clear risk factors for type 2 diabetes and cannot be ignored, type 2 diabetes in non-obese individuals is an important area of study and may reflect differences in pathophysiology (e.g., greater contribution of impaired insulin secretion relative to insulin resistance) and in other risk factors (e.g., low birthweight and *in utero* undernutrition) between those who are underweight/normal weight and those who are overweight/obese. Moreover, as levels of obesity continue to rise in India and China,[44–46] these countries will likely experience increased burdens in type 2 diabetes fueled by differing epidemics of underweight and overweight and influenced by differing pathophysiological mechanisms of type 2 diabetes development.

CONCLUSIONS AND OPPORTUNITIES FOR CHINA–INDIA COLLABORATION

The marked increase in the prevalence of type 2 diabetes in China and India over the past two decades is alarming. If efforts to address diabetes in these countries are not intensified, diabetes will continue to increase rapidly and become an even larger threat to health and economic development. Indeed, China and India face a formidable challenge, as addressing diabetes will require strengthening political will, identifying and scaling up effective interventions, generating new knowledge to guide programming and policy, creating sustainable financing solutions, and building human and institutional capacity. However, this common challenge, as well as similarities in the etiology and pathophysiology of type 2 diabetes, provides a great opportunity for China and India to join forces.

Drawing on existing evidence, China and India can pursue a unified agenda to implement proven interventions (e.g., prevention in high-risk groups, and delivery of high-quality care for people with diabetes) at scale.[47,48] It may also be mutually beneficial to pool human and institutional resources, share best practices for program and policy implementation, and come together to energize donors and key stakeholders from multilateral agencies, government and business. To fill knowledge gaps, China and India should consider establishing a diabetes research consortium to investigate the unique and emerging issues of importance in their countries, from novel risk factors to the pathophysiology of diabetes in Indian and Chinese populations. A partnership for research can also foster innovations in science and health care that could accelerate progress towards reducing type 2 diabetes.

Panel 1: Examples of opportunities for cross-country collaboration to address type 2 diabetes

Joint implementation and scale-up of evidence-based programs and policies:

- Implement lifestyle interventions to promote weight loss and healthy diet and physical activity. Randomized controlled trials in China (China Da Qing Diabetes Prevention Outcomes Study) and India (Diabetes Community Lifestyle Improvement Program Trial) have shown that lifestyle interventions reduce the incidence of type 2 diabetes in people with prediabetes.[47,49] China and India should now focus on the translation of lifestyle interventions into community settings to reach the broader population.
- Leverage primary care to prevent and control diabetes (e.g., implement diabetes screening to increase early detection of prediabetes and undiagnosed diabetes, link people with prediabetes to community-based lifestyle interventions, provide care coordination).[50] In India, for example, expanding the role of primary care in addressing diabetes can be achieved through the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke, which includes enhancing capacity of health-care systems to prevent, diagnose and treat diabetes as a key objective.
- Strengthen tobacco control policy (e.g., tobacco taxation, packaging and labeling of tobacco products, marketing restrictions) and expand tobacco cessation interventions, especially for males. Both China and India have ratified the WHO Framework Convention on Tobacco

Control (FCTC) and taken steps towards achieving the recommended actions. They should build on their progress and accelerate efforts to fulfill the FCTC requirements.
• Establish partnerships with those designing and managing cities and public spaces (e.g., business leaders, policymakers and community leaders) and ensure health is a priority in urban planning. *Healthy China 2030*, a national guideline issued by the government in 2016, includes a focus on promoting healthy lifestyles and physical fitness and provides a platform for prioritizing health in urban development.

Collaborative research and innovation:
• Examine the pathophysiology and etiology of type 2 diabetes in non-overweight individuals, including the role of impaired insulin secretion, low birthweight and *in utero* undernutrition.
• Investigate the role of novel risk factors, such as air pollution, noise pollution and persistent organic pollutants, in the development of type 2 diabetes.
• Conduct longitudinal studies to understand the role of the fetal environment on the development of type 2 diabetes and test interventions to improve maternal nutrition and prevent type 2 diabetes in offspring.
• Conduct implementation research to evaluate screening and control for diabetes in people with tuberculosis and *vice versa*, and to identify effective and cost-effective ways to carry out bidirectional screening in health-care settings.
• Carry out implementation research to evaluate the delivery, effectiveness and cost-effectiveness of scaling up lifestyle interventions for people at high risk for diabetes.
• Carry out implementation research to evaluate scaling up of high-quality, cost-effective diabetes care.
• Develop a joint research agenda focused on urbanization and type 2 diabetes, including the role of unplanned urbanization in fueling the diabetes epidemic and effective ways to create urban spaces that promote the public's health.
• Design and test strategies for creating healthier food environments and improving the availability and accessibility of healthy foods.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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